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19 APRIL 2000

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The Patent Office

The Patent Office
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Signed Andrew Craig

Dated 21 March 2000

Patents Form 1/77

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1/77



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The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — KR/NM/P32286

2. Patent application number
*(The Patent Office will fill in his part)* — 20 APR 1999 — **9909041.7**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

SmithKline Beecham plc
New Horizons Court, Brentford, Middx TW8 9EP.
Great Britain

Patents ADP number *(if you know it)* 5800974002

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention — Novel Pharmaceutical

5. Name of your agent *(if you have one)*

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SMITHKLINE BEECHAM PLC
TWO NEW HORIZONS COURT
BRENTFORD
MIDDLESEX TW8 9EP

Patents ADP number *(if you know it)* 5800974004

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

| Country | Priority application number *(if you know it)* | Date of filing *(day / month / year)* |
|---|---|---|

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

| Number of earlier application | Date of filing *(day / month / year)* |
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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

*a) any applicant named in part 3 is not an inventor, or*
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| | |
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| Continuation sheets of this form | |
| Description | 10 |
| Claim(s) | |
| Abstract | |
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| Priority Documents | |
| Translations of priority documents | |
| Statement of inventorship and right to grant of a patent *(Patents Form 1/77)* | |
| Request for preliminary examination and search *(Patents Form 9/77)* | |
| Request for substantive examination *(Patents Form 10/77)* | |
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11. We request the grant of a patent on the basis of this application

Signature K Rutter Date 20-Apr-99

12. Name and daytime telephone number of person to contact in the United Kingdom: K Rutter 01279 644396

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# NOVEL PHARMACEUTICAL

This invention relates to a novel pharmaceutical, to a process for the preparation of the pharmaceutical and to the use of the pharmaceutical in medicine.

European Patent Application, Publication Number 0,306,228 relates to certain thiazolidinedione derivatives disclosed as having hypoglycaemic and hypolipidaemic activity. The compound of example 30 of EP 0,306,228 is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (hereinafter also referred to as "Compound I").

International Patent Application, Publication Number WO94/05659 discloses certain salts of the compounds of EP 0,306,228 and in particular the maleic acid salt.

It has now been discovered that Compound I exists in the form of a novel hydrochloride salt which is dihydrated. This novel hydrochloride salt dihydrate (hereinafter also referred to as "Hydrochloride Hydrate") is particularly suitable for bulk preparation and handling. The novel form can be prepared by an efficient, economic and reproducible process particularly suited to large scale preparation.

The novel Hydrochloride Hydrate also has useful pharmaceutical properties and in particular it is indicated to be useful for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

Accordingly, the present invention provides 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, hydrochloride dihydrate characterised in that it:

(i) provides an infrared spectrum containing peaks at 3392, 2739, 1751, 1325 and 713 $cm^{-1}$; and/or

(ii) provides an X-ray powder diffraction (XRPD) pattern containing peaks at 9.1, 12.0, 15.7, 16.3 and 19.8 °2θ.

In one favoured aspect, Hydrochloride Hydrate provides an infra red spectrum substantially in accordance with Figure I.

In one favoured aspect, Hydrochloride Hydrate provides an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Figure II.

The present invention encompasses Hydrochloride Hydrate isolated in pure form or when admixed with other materials.

Thus in one aspect there is provided Hydrochloride Hydrate in isolated form.

In a further aspect there is provided Hydrochloride Hydrate in pure form.

In yet a further aspect there is provided Hydrochloride Hydrate in crystalline form.

The invention also provides a process for preparing Hydrochloride Hydrate, characterised in that 5-[4-[2-(N-methyl-N-(2-

pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (Compound I) is treated with aqueous hydrochloric acid and thereafter the required compound is recovered.

Suitably, the aqueous hydrochloric acid is formed by admixing concentrated hydrochloric acid and water or an aqueous solvent, such as aqueous denatured ethanol.

Suitably the reaction is carried out at ambient temperature but any convenient temperature may be employed which provides the required product.

Recovery of the required compound generally comprises crystallisation from an appropriate solvent such as diethyl ether or aqueous denatured ethanol.

Crystallisation and any re-crystallisation is generally carried out at low to ambient temperature, such as in the range of between 0 to 30°C for example 25°C; alternatively crystallisation may be initiated at an elevated temperature, such as in the range of between 30°C and 60°C for example 50°C, and then completed by allowing the temperature of the solvent to cool to ambient or low temperature, such as in the range of between 0 to 30°C for example 25°C. The crystallisation can be initiated by seeding with crystals of Hydrochloride Hydrate but this is not essential.

Compound I is prepared according to known procedures, such as those disclosed in EP 0,306,228 and WO94/05659. The disclosures of EP 0,306,228 and WO94/05659 are incorporated herein by reference.

When used herein the term 'prophylaxis of conditions associated with diabetes mellitus' includes the treatment of conditions such as insulin resistance, impaired glucose tolerance, hyperinsulinaemia and gestational diabetes.

Diabetes mellitus preferably means Type II diabetes mellitus.

Conditions associated with diabetes include hyperglycaemia and insulin resistance and obesity. Further conditions associated with diabetes include hypertension, cardiovascular disease, especially atherosclerosis, certain eating disorders, in particular the regulation of appetite and food intake in subjects suffering from disorders associated with under-eating ,such as anorexia nervosa, and disorders associated with over-eating, such as obesity and anorexia bulimia. Additional conditions associated with diabetes include polycystic ovarian syndrome and steroid induced insulin resistance.

The complications of conditions associated with diabetes mellitus encompassed herein includes renal disease, especially renal disease associated with the development of Type II diabetes including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

As mentioned above the compound of the invention has useful therapeutic properties: The present invention accordingly Hydrochloride Hydrate for use as an active therapeutic substance.

More particularly, the present invention provides Hydrochloride Hydrate for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

Hydrochloride Hydrate may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier. The formulation of Hydrochloride Hydrate is generally as disclosed for Compound (I) in the above mentioned publications.

Accordingly, the present invention also provides a pharmaceutical composition comprising Hydrochloride Hydrate and a pharmaceutically acceptable carrier therefor.

Hydrochloride Hydrate is normally administered in unit dosage form.

The active compound may be administered by any suitable route but usually by the oral or parenteral routes. For such use, the compound will normally be employed in the form of a pharmaceutical composition in association with a pharmaceutical carrier, diluent and/or excipient, although the exact form of the composition will naturally depend on the mode of administration.

Compositions are prepared by admixture and are suitably adapted for oral, parenteral or topical administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, pastilles, reconstitutable powders, injectable and infusable solutions or suspensions, suppositories and transdermal devices. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

Solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to

distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the active compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the active compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the active compound.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The present invention further provides a method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of Hydrate to a human or non-human mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

In a further aspect the present invention provides the use of Hydrochloride Hydrate for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

In the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof Hydrochloride Hydrate may be taken in doses, such as those described in EP 0,306,228 and WO94/05659.

No adverse toxicological effects are indicated in the above mentioned treatments for the compounds of the invention.

The following examples illustrate the invention but do not limit it in any way.

Preparation of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, hydrochloride dihydrate

**Example 1:** 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (4 g) was suspended in water (25 ml), and concentrated hydrochloric acid (4 ml) was added , forming a clear solution, and then a thick suspension. After 1 hour the suspension was diluted with water (10 ml), the crude product was filtered and then washed with denatured ethanol (20 ml). The crude product was stirred in diethyl ether (50 ml), filtered and dried at 50°C to afford the title compound(3.1 g ,63%).

**Example 2:** 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (4 g) was suspended in denatured ethanol (40 ml), and concentrated hydrochloric acid (4 ml) was added, forming a solution. Water (40 ml) was added, and the resulting suspension was cooled to 0°C and stirred for 3 hours. The product was filtered, washed with acetone (2 x 10 ml) and dried at 50°C to afford the title compound- (3.91 g,82%).

**CHARACTERISING DATA:** The following characterising data were generated for Hydrochloride Hydrate:

**A Water content**

This was determined as 8.4% w/w using a Karl Fischer apparatus (theory for dihydrate 8.37% w/w).

**B Ionic Chlorine**

This was determined as 8.5% w/w (theory for dihydrate 8.26% w/w).

**C Infrared**

The infrared absorption spectrum of a mineral oil dispersion of Hydrochloride Hydrate was obtained using a Nicolet 710 FT-IR spectrometer at 2 $cm^{-1}$ resolution. Data were digitised at 1 $cm^{-1}$ intervals. The spectrum obtained is shown in Figure I. Peak positions are as follows: 3392, 3139, 3094, 2739, 1758, 1751, 1706, 1643, 1632, 1610, 1583, 1545, 1513, 1412, 1357, 1325, 1297, 1265, 1251, 1216, 1179, 1152, 1138, 1110, 1080, 1053, 1033, 1010, 985, 953, 931, 909, 827, 822, 812, 769, 739, 724, 713, 660, 620, 604, 593, 562, 539, 529 and 508 $cm^{-1}$.

**B X-Ray Powder Diffraction (XRPD)**

The XRPD pattern of Hydrochloride Hydrate is shown below in Figure II and a summary of the XRPD angles and calculated lattice spacings characteristic of Hydrochloride Hydrate is given in Table I.

A Bruker AXS D8 Advance X-ray powder diffractometer (Cu X-ray source) was used to generate the pattern using the following acquisition conditions:

| | |
|---|---|
| Tube anode: | Cu |
| Generator tension: | 40 kV |
| Generator current: | 40 mA |
| Start angle: | 2.0 °2θ |
| End angle: | 35.0 °2θ |
| Step size: | 0.02 °2θ |
| Time per step: | 2.5s |

**Table I.**

X-Ray Powder Diffraction Angles and Calculated Lattice Spacing Characteristic of Hydrochloride Hydrate.

| Diffraction Angle (°2θ) | Lattice Spacing (Angstroms) |
|---|---|
| 9.1 | 9.75 |
| 12.0 | 7.37 |
| 15.7 | 5.64 |
| 16.3 | 5.42 |
| 18.2 | 4.88 |
| 18.6 | 4.77 |
| 19.8 | 4.48 |
| 20.9 | 4.24 |
| 21.6 | 4.11 |
| 22.8 | 3.89 |
| 24.1 | 3.69 |
| 24.7 | 3.60 |
| 25.4 | 3.50 |
| 26.0 | 3.42 |
| 27.5 | 3.24 |
| 27.7 | 3.21 |
| 28.7 | 3.11 |
| 31.4 | 2.84 |
| 31.6 | 2.83 |
| 32.1 | 2.79 |
| 33.1 | 2.71 |
| 33.6 | 2.66 |
| 34.6 | 2.59 |

Figure I. Infrared Spectrum of Hydrochloride Hydrate.

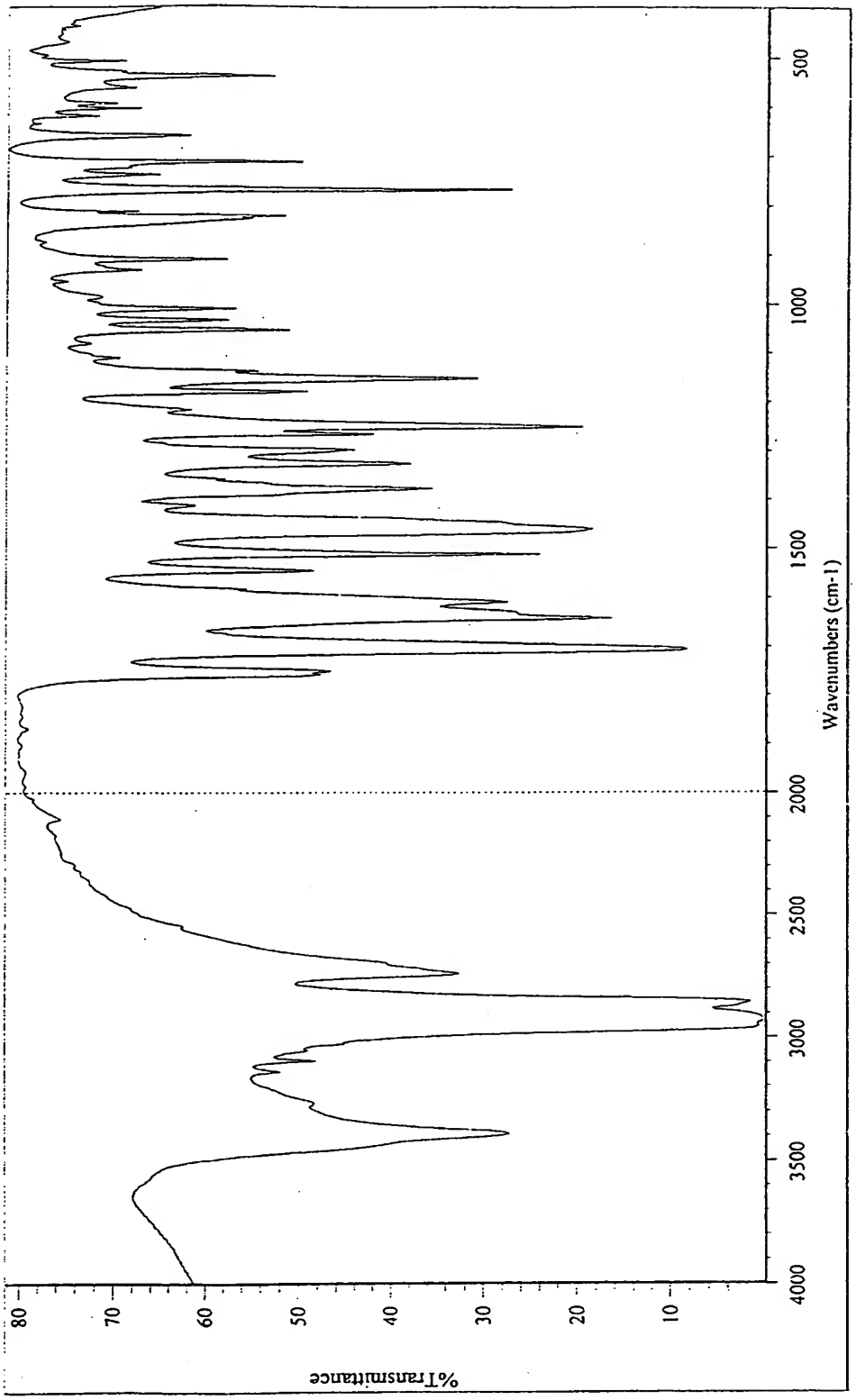

Figure II. X-Ray Powder Diffraction Pattern of Hydrochloride Hydrate